IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

THE PROCTER & GAMBLE COMPANY, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	)	Civil Action No. 04-940 (JJF)

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S POST-TRIAL REPLY BRIEF

January 26, 2007

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INTRODUCTION

P&G's principal argument is that risedronate would not have been obvious in view of the almost identical compound, 2-pyr EHDP. P&G's argument rests on the assumption that the person of ordinary skill in the art could not connect the dots, even if they were the only two dots on the page. In particular, P&G relies on an expert with no experience in medicinal chemistry or drug discovery, whose testimony boils down to the proposition that ordinary skill in the art is tantamount to petrified-with-fright mental paralysis. By all accounts, however, skill in the art here consists of the highest levels of education, experience, curiosity and scientific skill. To persons having such qualifications, nothing would have been more obvious than making the minor change to molecular structure that characterizes the difference between 2-pyr EHDP and risedronate.

Here, P&G patented a use of 2-pyr EHDP in the'406 patent. That patent has expired. With the '122 patent at issue in this case, P&G seeks an extension of the monopoly of the '406 patent by claiming the 2-pyr EHDP compound and *all* its therapeutic uses, including a claim (claim 21) that covers the very use that is claimed in the '406 patent. P&G also seeks to extend and expand that monopoly by claiming risedronate, the near-clone of 2-pyr EHDP, together with all of its uses. The asserted claims of the '122 patent are therefore invalid for nonstatutory, or obviousness-type, double patenting. Moreover, since P&G failed to prove an early enough invention date for the asserted claims, the '406 patent is prior art, and those claims are invalid for statutory obviousness as well.

I. P&G MISCHARACTERIZES THE BURDENS OF PROOF

As a threshold matter, P&G's statement of Teva USA's burden in this case is not correct. (P&G Br. at 11) (D.I. 100). Although courts often say that the challenger must prove "invalidity" by clear and convincing evidence, that statement is imprecise. The presumption of validity of a patent under 35 U.S.C. § 282 is a procedural device that places on the party asserting invalidity the initial burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 291 (Fed. Cir. 1985). Once a prima facie case has been established, the burden then shifts to the patentee to go forward with rebuttal evidence showing facts supporting non-obviousness. *Id.* at 291-92. The Court must consider all facts relevant to the issue of obviousness, both the facts established by the party asserting invalidity and those established by the rebuttal evidence submitted by the patentee. *Id.* at 293.

Teva USA's burden in the present case is, at most, to prove certain *facts* demonstrating invalidity by clear and convincing evidence. *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1377 (Fed. Cir. 2002). Indeed, with respect to other critical fact issues, P&G bears the burden, not Teva USA. Thus, if Teva USA establishes the filing date of the '406 patent by clear and convincing evidence (which it has, because that date is documented and undisputed), P&G must establish that its inventors conceived their invention before that date and that they diligently reduced it to practice. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996). If Teva USA establishes the facts demonstrating that risedronate was prima facie obvious, to the extent that P&G seeks to rely on alleged unexpected properties of risedronate compared to 2-pyr EHDP, it is P&G

that must demonstrate those facts, and Teva USA is not required to prove the negative. *Burlington Indus., Inc. v. Quigg*, 229 U.S.P.Q. 916, 918 (D. D.C. 1986), *aff'd*, 822 F.2d 1581 (Fed. Cir. 1987).

The primary facts that are essential to Teva USA's case are set forth for the most part in documents, the authenticity and accuracy of which P&G does not dispute: the '122 patent, the '406 patent, other scientific publications and P&G's laboratory records. Accordingly, the Court's principal task is to determine whether, based on the evidence, the asserted claims are invalid either for obviousness-type double patenting or for obviousness, both of which are questions of law as to which neither party bears a burden of proof. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1566-68 (Fed. Cir. 1987).

Moreover, the principal reference, both for double patenting and for obviousness, is the '406 patent. As far as the record demonstrates, the examiners responsible for issuing the '122 patent were unaware of the '406 patent; the examiners did not locate the '406 patent in their searches, and P&G's attorneys never advised them of its existence or content. Because the examiners never considered the '406 patent, the presumption of validity of the '122 patent is more easily overcome. *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 714 (Fed. Cir. 1984) ("Deference is due the Patent and Trademark Office decision to issue the patent with respect to evidence bearing on validity which it considered but no deference is due with respect to evidence it did not consider."); *EWP Corp v. Reliance Universal Inc.*, 755 F.2d 898, 905 (Fed. Cir. 1985).

II. DR. LENZ IS HIGHLY QUALIFIED; IN FACT, HE IS MORE QUALIFIED THAN DR. MCKENNA

A. Dr. Lenz's Experience as a Medicinal Chemist Qualifies Him as an Expert With Eespect to the Issues in This Case

P&G's first line of defense is to attack the messenger, Dr. Lenz. All of the evidence at trial demonstrated that Dr. Lenz had the ideal qualifications to opine on the issues about which he testified – the obviousness of risedronate. Certainly, he is by any measure more qualified that P&G's corresponding expert, an academic with no contemporaneous experience or background in the real world of this case – the design and development of new drugs in the mid-1980s.

This case involves the discovery and development of new pharmaceutical compounds. (JTX1, col. 1, ll. 26-53; Lenz 68, 74.) According to P&G, 2-pyr EHDP and risedronate were first made by a Ph.D. chemist working in the laboratory of a pharmaceutical company. That exact environment is where Dr. Lenz spent most of his career. (Lenz 50, 63, 67.) He did not work in a university, and he did not carry out basic research on new chemical syntheses. (DTX134.) Instead, his career involved discovering new drugs in a wide variety of therapeutic areas. (Lenz 50, 57-58.) Dr. Lenz knows that environment; he knows how people actually making new drugs think; he knows what they do when they go to work in the morning; he knows how the business of drug discovery and design is conducted. (Lenz 56-59, 63.) Even more important, he knows that environment as it existed in 1985 because he was there. (Lenz 67; McKenna 637.)

Dr. Lenz started his professional career in drug discovery in 1969, working on antihypertensive drugs. (Lenz 57.) He next worked on steroidal drugs and on birth

control drugs, then on central nervous system agents. (Lenz 57-58.) He then moved to another firm, where he directed research into a variety of new pharmaceutical compounds. (Lenz 59-60.) Later, he was involved in new drug screening and drug discovery technologies. (Lenz 62-63.) At the time P&G first made 2-pyr EHDP and risedronate, Dr. Lenz already had 15 years of experience in the field of drug discovery and development. (Lenz 95; McKenna 637.) He has written three books, the titles of which reflect his qualifications: *Current and Future Trends in Drug Discovery*; *From Data to Drugs: Strategies for Benefiting from the New Drug Discovery Technologies*; and *The Opiates*. (DTX134; Lenz 64-65.) His list of publications includes many papers whose titles make clear that he is uniquely qualified to opine on the skill in the drug discovery art. (DTX134 at 4-10.)

Dr. Lenz's qualifications are certainly more to the point than Dr. McKenna's. P&G notes that the '122 patent relates to "pharmaceutical compositions containing geminal bisphosphonates." (P&G Br. at 14.) Dr. McKenna's qualifications trip over the first two words. In contrast to Dr. Lenz, Dr. McKenna has no experience in the pharmaceutical industry. (PTX430.) His entire career has been spent in academia. (McKenna 539, 541.) He candidly admitted that as of 1985, he was not and had never been involved in drug discovery and design in any way. (McKenna 639-46.) He has no first hand knowledge of the drug discovery and design process in the industrial setting. He has no idea how people in the field work, how they think, how they make choices of ideas to pursue, what motivates them to carry out experiments, or what their expectations are when carrying out those experiments. More importantly, he has no understanding of the environment as it existed in 1985, because he was not there. (McKenna 638.)

B. The Specialty of Organophosphorus Chemistry Is Irrelevant

P&G attempts to deflect attention from Dr. McKenna's shortcomings by touting his knowledge of phosphorus chemistry, and noting that the claimed compounds contain phosphorus atoms. Of course, in addition to phosphorus atoms, every compound claimed in the '122 patent includes at least one nitrogen atom (DTX305), but P&G does not suggest that the person skilled in the art must be an expert in nitrogen-containing compounds, or an expert in oxygen-containing compounds because they all contain oxygen atoms as well. The specialty of organophosphorus chemistry is irrelevant for several reasons.

First, Dr. McKenna's work with bisphosphonates for drug applications did not begin until long after the relevant time. (McKenna 638, 642, 644-45.) To the extent that his research interests dealt with bisphosponates at all prior to 1985, they resulted in a single paper, which described a new synthetic reaction, not any new compounds for pharmaceutical use.[1] (McKenna 640.) Moreover, his interest in bisphosphonates during the relevant era was at most as an "observer." (McKenna 635.) That is, Dr. McKenna presumably observed the literature and saw what others were doing in the field. According to P&G, that he was an observer with no actual experience makes him qualified to opine as a person skilled in the art. Yet P&G claims that Dr. Lenz, who likewise had no actual experience with bisphosphonates, is not qualified, even though his experience in drug design and discovery vastly exceeds that of Dr. McKenna. In fact, as

[1] Although Dr. McKenna's paper was published in 1977 (McKenna 638), it apparently had no impact on how bisphosphonate drugs are made. The inventors of the use of alendronate disclosed their own synthetic method (DTX76; Lenz 108-10), which Dr. Benedict then adapted to make risedronate. (DTX150 at PG45560.) Neither the alendronate inventors nor Dr. Benedict anywhere referred to Dr. McKenna's work.

Dr. Lenz pointed out, experienced medicinal chemists were frequently were assigned new therapeutic areas to explore. (Lenz 50, 56-58, 202.) Under such circumstances, they did their homework exactly as Dr. Lenz did: they studied the literature and learned the biology and chemistry related to the particular field of endeavor to which they were assigned. (Lenz 56-59.) Thus, prior experience in a specific therapeutic area is not critical; what is critical, however, is the experience in drug discovery, which is what the case is about.

Second, it is undisputed that the research effort in this area did not involve organophosphorus chemistry. (Lenz 79.) The phosphorus-containing part of the bisphosphonate molecule, the "head," varied little from compound to compound because by 1985 those in the art were already aware that the best results were likely to be observed if the R_1 group was hydroxy. (McKenna 669; Lenz 69-70.) Indeed, as Dr. McKenna conceded, the phosphorus-containing portion of the molecule is identical in every bisphosphonate drug ever sold in the United States (etidronate, pamidronate, alendronate, risedronate, and ibandronate). (McKenna 649; DTX305.) On the other hand, the part of the molecule that varied from product to product, and which chemists modified to make new products, did not include phosphorus and therefore did not implicate organophosphorus chemistry. (Lenz 72, 79.)

Third, the organophosphorus chemistry involved was not complex. The creation of the bisphosphonate head of the molecule was a straightforward synthesis, disclosed in the literature, which required only a single step. (Lenz 109-11; DTX76; DTX150 at PG45560.) Indeed, according to Dr. Benedict, the chemist could simply pour the

chemicals together, set the temperature, walk away and return when the reaction was finished. (Benedict 512.)

Finally, although Dr. Lenz had not worked with bisphosphonates for pharmaceutical uses (neither had Dr. McKenna before 1985), his testimony makes clear that he had worked extensively with phosphorus chemistry. (Lenz 287-88.) That is, his drug development work required that he make new phosphorus-containing compounds, whether or not he regarded himself as a specialist in the field. (Lenz 288.)

P&G's effort to define ordinary skill in the art as including specific expertise in organophosphorus chemistry is nothing more than an effort to denigrate the vast experience and skills of Dr. Lenz and to prop up the dubious credentials of Dr. McKenna. In fact, it is Dr. McKenna, not Dr. Lenz, who lacks the experience necessary to place the Court at the relevant place at the relevant time. In view of Dr. McKenna's absence of temporally relevant experience in drug discovery and design, his opinions on what would have been obvious to people actually in the field are entitled to little weight.

P&G asserts that in *Merck & Co. v. Teva Pharmaceuticals, Inc.*, 228 F. Supp. 2d 480 (D. Del. 2002), *aff'd*, 347 F.3d 1367 (Fed. Cir. 2003), this Court adopted a different of ordinary skill in the art definition from Teva USA's proposal here. First, contrary to P&G's representation, the patent in that case did not "claim alendronate." (P&G Br. 15.) In fact, at the time of the application for that patent, alendronate was an old compound, having first been disclosed in the prior art years before. (DTX42.) Thus, the patent did not claim the compound, but instead merely claimed its use "for treatment of urolithiasis [kidney stones] and inhibiting bone reabsorption." (DTX42, claim 1.) The patent therefore did not involve either drug discovery or the conception of new chemical

compounds. In any event, the definition the Court adopted in that case (quoted at P&G Br. 16) is not materially different from that proposed by Dr. Lenz. Contrary to P&G's contention here, the Court in *Merck* did not require specific expertise in "organophosphorus chemistry," and neither of Merck's experts in that case had any specialized training in that field. Instead, the only specific experience the Court's definition required was that the person skilled in the art be "exposed to" knowledge about bone metabolism agents. Thus, as Dr. Lenz pointed out, his definition of the person of skill in the art who was tasked with investigating new bisphosphonates would subsume the Court's definition in *Merck* because

> if you're going to work in a particular area you're going to inform yourself, that's an advantage of being a chemist, you can work in many areas in the therapeutic fields. If you're going to work in osteoporosis, you're going to familiarize yourself with both the biology and chemistry at the time.

(Lenz 202.)

Courts faced with similar questions have never defined the person skilled in the art in such a circumscribed fashion as P&G suggests, because they recognize that in the art of drug discovery, the skills are transferable from one therapeutic area to another. *See, e.g.*, *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (obviousness of psychotropic drug amitriptyline: person skilled in the art was a medicinal chemist with knowledge of techniques used in the field of drug design; no specific experience in psychotropic drugs required); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 846 (S.D. Ind. 2005), *aff'd*, 2006 U.S. App. LEXIS 31748 (Fed. Cir. Dec. 26, 2006) (obviousness of olanzapine, active ingredient in Zyprexa®: person skilled in the art is a "scientist with a Ph.D. in medicinal chemistry, pharmacology, or a similar

discipline"; no special training in class of drugs required); *Pfizer Inc. v. Ranbaxy Laboratories Ltd.*, 405 F. Supp. 2d 495, 516 (D. Del. 2005), *aff'd in part and rev'd in part*, 457 F.3d 1284 (Fed. Cir. 2006) (obviousness of atorvastatin, active ingredient in Lipitor®: ordinary skill in the art includes no more than "general knowledge" of statins, not specialized training); *Sanofi-Synthelabo v. Apotex Inc.*, 2006 WL 2516486 at 14 (S.D.N.Y. Aug. 31, 2006), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006) (obviousness of clopidogrel sulfate, active ingredient in Plavix®: person skilled in the art would have experience "in the synthesis, study and properties of drugs, drug candidates, and biologically active compounds"; no specialized training in the type of drugs at issue required); and *Mead Johnson & Co. v. Premo Labs.*, 207 USPQ 820, 841 (D. N.J. 1980) (obviousness of isoxuprine, active ingredient in Vasodilan®: person skilled in the art possessed a Ph.D. in organic chemistry, a "deep interest in medicinal chemistry" and an awareness of the techniques of drug design; no special experience in class of drugs required).

In fact, as the above cases make clear, it is Dr. McKenna, not Dr. Lenz, whose experience does not measure up. At the relevant time, Dr. McKenna would not have qualified under any of the standards set forth above. Indeed, Dr. McKenna's lack of experience in medicinal chemistry was highlighted by his and P&G's exemplary reference to the drug thalidomide. Attempting to demonstrate that what he called "small changes" in molecular structure can result in major changes in therapeutic properties, Dr. McKenna made much of his understanding that one enantiomer of thalidomide was therapeutically active, while the other caused birth defects. (McKenna 602.) Dr. Lenz, however, pointed out more recent evidence demonstrating that in fact the enantiomers of

thalidomide "racemize" in the body, so that the activities of the two enantiomers cannot be separated. (Lenz 214.) *See Sanofi-Synthelabo*, 2006 WL 2516486 at 12 ("Ibuprofen, Thalidomide and Pesugryl are all examples of drugs that racemize in the body."). Apparently, because of his limited background in medicinal chemistry, Dr. McKenna was not aware of the current state of knowledge.

C. Dr. Lenz Qualifies as an Expert under Federal Rule of Evidence 702

Finally, P&G's argument that Dr. Lenz does not qualify as an "expert" is absurd. In the Third Circuit, Federal Rule of Evidence 702 is interpreted to require "three distinct substantive restrictions on the admission of expert testimony: qualifications, reliability, and fit." *Elcock v. KMart Corp.*, 233 F.3d 734, 741 (3d Cir. 2000); *In re Paoli Railroad Yard PCB Litigation*, 35 F.3d 717, 741-43 (3d Cir. 1994).[2] "Reliability" relates to the scientific foundation of the testimony, and "fit" requires that the testimony assist the trier of fact, i.e., that it relate to the disputed issues and be helpful in resolving them. *ID Sec. Sys. Can., Inc. v. Checkpoint Sys., Inc.*, 198 F. Supp. 2d 598, 602-03 (E.D. Pa. 2002).

P&G does not challenge the scientific reliability of Dr. Lenz's testimony, nor does it assert that his testimony cannot assist the trier of fact. P&G's only challenge is to Dr. Lenz's qualifications. In this Circuit, the qualification requirement is interpreted "liberally" to encompass "a broad range of knowledge, skills, and training." *Id.* at 602. Recently, in *Pfizer, Inc. v. Mylan Laboratories, Inc.*, 2006 U.S. Dist. LEXIS 83856 at *9-10 (W.D. Pa. Nov. 17, 2006), the patent related to a pharmaceutical formulation, but the expert was a synthetic chemist, not a formulation scientist. The court denied a motion *in*

[2] Because the standard for deciding whether an expert witness is qualified is not specific to patent law, Third Circuit law applies. *Micro Chem., Inc. v. Lextron, Inc.*, 317 F.3d 1387, 1391 (Fed. Cir. 2003).

limine to disqualify the expert. It noted that "[t]he requirements of Rule 702 'mandate[s] a policy of liberal admissibility," *quoting Paoli*, *supra*, and then stated:

> Given that "a broad range of knowledge, skills, and training qualify an expert as such," and the liberal standards under Rule 702, the Court finds and rules that Dr. Burgess meets the first requirement of Rule 702.

Id. at *5, 9-10 (*quoting Paoli*, *supra*). *See also Schneider v. Fried*, 320 F.3d 396, 407 (3d Cir. 2003) (expert qualified despite lack of experience in "sub-specialty" at issue); *Tristrata Tech., Inc. v. Mary Kay, Inc.*, 423 F. Supp. 2d 456, 463-64 (D. Del. 2006) (applying *Paoli*, *supra*, in patent context); *eSpeed, Inc. v. Brokertec USA, L.L.C.*, 404 F. Supp. 2d 575, 579-80 (D. Del. 2005). Here, Dr. Lenz's qualifications include a sophisticated scientific background and a contemporaneous knowledge and experience in the pharmaceutical industry in general and in the field of drug discovery and design in particular. His curriculum vitae demonstrates the depth and breadth of his relevant knowledge, and his testimony at trial showed his acquired knowledge and understanding of the specifics of the case. Indeed, to the extent that any expert's qualifications to testify as to the state of the drug discovery art in 1985 are suspect, it is those of Dr. McKenna, whose only claim to specific expertise is his essentially irrelevant contemporaneous interest in phosphorus chemistry.

III. THE ASSERTED CLAIMS OF THE '122 PATENT ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Obviousness-type Double Patenting is Not "Redundant"

The obviousness-type double patenting issue is not "redundant" in this case. Although the substantive inquiry is similar to that involved in the statutory obviousness analysis, P&G understates the differences between them. The objects of comparison are

different in two key respects. First, the obviousness-type double patenting inquiry is limited to comparing the claimed invention at issue to an invention claimed in an earlier patent, in view of the prior art. Statutory obviousness, in contrast, compares the claimed invention at issue to the entirety of the prior art. Second, a § 103 obviousness analysis can include consideration of objective criteria suggesting non-obviousness, also termed "secondary considerations," while such criteria are not considered in an obviousness-type double patenting analysis. *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 n.1. P&G's arguments concerning long-felt need, commercial success, and unexpected results, even if supported, do not influence the obviousness-type double patenting analysis.

The obviousness-type double patenting analysis further simplifies this case because there are no invention date issues to resolve. The '406 patent was the first patent filed and the first patent issued. P&G has stipulated that asserted claims 4, 16, and 23 of the '122 patent do not have written description support in any application filed prior to the application which led directly to the '122 patent. (D.I. 86 at ¶3). Therefore, even if the Court finds that the '406 patent is not prior art to the '122 patent, the asserted claims of the '122 patent can still be invalid for obviousness-type double patenting based on claim 15 of the '406 patent. *See Eli Lilly & Co. v. Barr Labs.*, 251 F.3d 955, 973 (Fed. Cir. 2001 ("[d]ouble patenting is thus applied when neither patent is prior art against the other").

B. P&G Misstates the Legal Standard for Obviousness-Type Double Patenting

P&G argues that claim 15 of the '406 patent and the asserted claims of the '122 patent are "patentably distinct," but fails to define this phrase in the appropriate context.

The determination of patentable distinctness is simply the determination of whether the claimed invention of the second patent (the '122 patent) would have been obvious from the claimed invention of the first patent (the '406 patent). *In re Longi*, 759 F.2d 887, 893 (Fed Cir. 1985). The analysis is similar to that applied in conventional obviousness cases (except that secondary considerations are not pertinent). *Eli Lilly & Co.*, 251 F.3d at 968. Thus, characterizing claim 15 as a claim to a "dosing regimen" or focusing on the "heart" of the claimed invention begs the question: to a person skilled in the art, would the inventions of the asserted claims of the '122 patent have been obvious in view of the invention claimed in claim 15 of the '406 patent?

P&G cites two cases, *General Foods Corp. v. Studiengessellschaft Kohle*, 972 F.2d 1272 (Fed. Cir 1992), and *Carman Indus., Inc. v. Wahl*, 724 F.2d 932 (Fed. Cir. 1983), for the proposition that double patenting is determined by analysis of the claims "as a whole." (P&G Br. at 47.) This axiom applies to all patent claim issues, and is beyond dispute. *See Eli Lilly & Co.*, 251 F.3d at 968. Neither Teva USA nor its expert suggested otherwise.

General Foods and *Carman*, however, after stating the above truism, apply a legal test that has no bearing here. Both cases apply a two-way test for obviousness-type double patenting, as distinguished from a one-way test, which applies here. *See In re Berg*, 140 F.3d 1428, 1432 (Fed. Cir. 1998). The facts that trigger the one-way test are the facts in this case: the application for the patent containing the reference claim (claim 15 of the '406 patent) was filed before the application for the patent containing the asserted claims (claims 4, 16 and 23 of the '122 patent), and the reference patent issued first. As the name implies, the one-way test involves one step: the asserted claim is

invalid if the claimed invention would have been obvious in view of the invention of the reference claim. *See id.*

On the other hand, the two-way test of *General Foods* applies when the patents issue out of filing order. That is, if the asserted patent was filed for before the reference patent, but because of the PTO's delays, it issued later, then the asserted claim will only be held invalid if the claims "cross-read," *i.e.*, the invention of the asserted claim would have been obvious in view of the invention of the reference claim, *and* vice-versa. *See In re Braat*, 937 F.2d 589 (Fed. Cir. 1991).

In *General Foods*, the court found that a later-issued claim to a one-step process for decaffeinating coffee was not invalid in view of an earlier-issued claim to a two-step process of (1) decaffeinating coffee and (2) recovering the caffeine. In other words, a later-issued claim to a single step process was not invalid based on an earlier-issued claim to a two-step process, in which one of the steps was the single step in the later-issued claim. The challenged claims, directed to a process for decaffeinating coffee beans, were filed in January 1971. *General Foods*, 724 F.2d at 1275. The reference claim, directed to a process of decaffeinating coffee and recovering the caffeine, issued in April 1974. *Id.* Since the applicant filed the challenged claims *before* the reference claim, but their issuance was delayed by the need to prosecute an appeal within the PTO, *id.*, the two-way test applied. *See id.* (describing the long prosecution required to obtain allowance of the challenged claims). That is not the case here. Here, the claims issued in the order in which they were filed: the '406 patent application was filed before the '122 patent application was filed and the '406 patent issued before the '122 patent issued. Under

such circumstances the one-way test applies: would the claimed invention of the '122 patent have been obvious in view of the invention of claim 15 of the '406 patent?

The *Carman* case, cited by P&G, dealt with another rare scenario in which the claims at issue were in a utility patent, and the reference claim was in a design patent. 724 F.2d at 941. The Federal Circuit applies a two-way test in that special situation because of "the differences in subject matter with which each type of patent is concerned." *Id.* at 939; 3A Donald S. Chisum, Chisum on Patents § 9.03[3][d] (2006) (stating that "the rational in *Carman* focuses on the particular problems of applying double patenting to two types of patents (utility and design) that cover fundamentally different types of subject matter"). Where the claims at issue are in a design patent and a utility patent, the obviousness-type double patenting test applied "is whether the subject matter of the claims of the patent sought to be invalidated would have been obvious from the subject matter of the claims of the other patent, and vice versa": a two-way test. *Id.* at 941. Thus, the obviousness-type double patenting analysis in *Carman* does not apply here.

The "one-way" cases, which apply here, do not support P&G, and do not preclude the application of obviousness-type double patenting merely because the claims cover different kinds of subject matter. In *Geneva Pharmaceuticals*, the reference claims (in the Crowley patent) were to a pharmaceutical container holding tablets of a particular drug and desiccant. 349 F.3d at 1382-83. The claims under attack (in the '354 and '552 patents) were more broadly drawn to the drug *per se*. *Id.* The Court held the drug claims invalid. *Id.* at 1384. The court reiterated the long-recognized principle that a claim to a method of using a compound is not patentably distinct from a claim to the compound

itself in a patent disclosing the identical use. *See id.* at 1385-86 (citing *In re Byck*, 48 F.2d 665, 666 (C.C.P.A. 1931), and *In re Christmann*, 128 F.2d 596 (C.C.P.A. 1942)). Thus, the double patenting inquiry boils down to the issues that the parties tried: would the subject matter of claims 4, 16 and 23 of the '122 patent have been obvious to a person skilled in the art who was aware of the claimed invention of the '406 patent.

C. The Subject Matter of the Asserted Claims of the '122 Patent Would Have Been Obvious in View of Claim 15 of the '406 Patent

1. Risedronate Would Have Been Obvious in View of the Structure and Properties of 2-Pyr EHDP

Courts have long recognized and continuously affirmed the proposition that compounds with similar structures can be presumed to have similar properties. *In re Merck*, 800 F.2d at 1096 ("structural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties", *quoting In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979)).

Apparently recognizing the force of this doctrine, P&G makes the conclusory statement that "while 2-pyr EHDP and risedronate may appear similar on paper in two dimensional depictions, multiple structural differences exist in 3-dimensions." (P&G Br. at 21.) P&G, however, cites no evidence showing that the two-dimensional representations that both sides used to illustrate the compounds in any way distort or overemphasize the structural similarities between them. P&G does not point out a single difference apparent from a three-dimensional representation that is not fairly indicated by the two-dimensional illustrations. More to the point, P&G points to no such difference that would have been important to a person of ordinary skill in the art. Indeed, risedronate and 2-pyr EHDP have the same molecular components that such persons

recognized as contributing to the properties of bisphosphonates, arranged in virtually the same way. The only difference, the position of the pyridyl group, is reflected in the two dimensional structures. Had the third dimension been significant, P&G could have presented it at trial, rather than have its lawyers argue about it in post-trial submissions. Indeed, it is not surprising that later in its brief P&G admits that the differences between the two are slight, describing 2-pyr EHDP as the "structurally similar positional isomer" of risedronate. (P&G Br. at 41.)

P&G also asserts that because of these unidentified three-dimensional differences, the compounds have "vastly" different physical, chemical and biological properties. (P&G Br. at 21). Nothing in record supports that statement. Even its own experts said no such thing; in fact, they identified no differences in physical or chemical properties. With respect to biological properties, as discussed *infra*, the totality of the evidence showed them to be remarkably similar. (McKenna 659-60, 674).

P&G states that the properties of risedronate and 2-pyr EHDP "could" be different (P&G Br. at 21), but fails in the end to identify any actual differences between the properties of these two compounds that would not have been reasonably expected based on the structures and properties of known prior art compounds. More important, P&G failed to demonstrate why one of ordinary skill in the art seeing 2-pyr EHDP would not have been motivated to modify that compound with a reasonable expectation of success in achieving similar properties with risedronate.

Indeed, P&G has not identified a single instance in which a court has declined to find that two compounds as closely related to each other as 2-pyr EHDP and risedronate, and useful for the identical application, were not prima facie obvious from each other.

This consistency is especially apparent in cases in which the compounds were, as here, positional isomers. (*See* Teva USA Br. 31-32 and cases cited.) On the other hand, in every case P&G cites in which a compound was held patentable over its positional isomer (P&G Br. at 22), patentability was based not on findings that the compounds were not prima facie obvious, but instead on the fact that the new compound exhibited highly unexpected beneficial properties compared to the prior art. As discussed in Teva USA's brief at 32-41 and Proposed Findings of Fact (¶¶ 93-123), P&G cannot make that showing here.

2. The '406 Patent Would Not Have Taught Away From Modifying 2-pyr EHDP to Make Risedronate

P&G agrees that the '406 patent is relevant because "[t]he '406 patent and the '122 patent are directed to the same problem, namely the impairment of bone mineralization cause by long-term use of bisphosphonates." (P&G Br. at 22.) However, P&G's argument that the '406 patent "teaches away" from modifying the 2-pyr EHDP compound is both irrelevant to double patenting and fails to consider the patent from the viewpoint of a person of ordinary skill in the art.

Double patenting requires a comparison of the claimed invention of the '406 patent with that of the '122 patent. Claim 15 of the '406 patent does not teach away from anything. It describes a treatment for osteoporosis that involves administering a compound selected from a group of eight. The claim itself discloses that 2-pyr EHDP is the most potent compound of the group by a factor of at least ten. (JTX5.) Thus, the claim establishes the lead compound that a person of ordinary skill would begin with. (McKenna 681-84; Lenz 89.) Nothing in the claim suggests any toxicity issues with 2-pyr EHDP; on the contrary, the fact that the inventors specifically claimed 2-pyr EHDP

suggests that it is safe and effective for its claimed use – treating osteoporosis. (McKenna 684-85.)

Even considering the entirety of the specification of the '406 patent (necessary for the *obviousness* analysis, but not for the *obviousness-type double patenting* issue), the perspective is that of the person of ordinary skill. Under either party's definition, the person of ordinary skill is a chemist. Therefore, P&G's arguments that the '406 patent discloses an intermittent dosing regimen, discloses multiple compounds in addition to 2-pyr EHDP, and provides assay data indicating a dose at which 2-pyr EHDP was "lethally toxic," should be considered from the viewpoint of a chemist in the field in the mid-1980s. From that perspective, the '406 patent would provide a motivation to modify the compound 2-pyr EHDP to make risedronate, with a reasonable expectation of success. (Lenz 95-97.)

3. The '406 Patent Discloses More Than Just a Dosing Regimen – It Discloses a Method of Treating Osteoporosis Using Bisphosphonates

After accusing Teva USA of focusing on only a single aspect of the '406 patent, the 2-pyr EHDP compound, P&G narrowly focuses only on the intermittent dosing regimen described in the '406 patent, calling it the "heart" of that patent. (P&G Br. at 22.) This myopic view contradicts P&G's own prior admonition, a few pages earlier, which explains that courts should consider each prior art reference "in [its] entirety" and "as a whole," because each reference is "relevant for all that it teaches to those of ordinary skill in the art" "not only for what it expressly teaches, but also for what it fairly suggests." (P&G Br. at 22, *quoting In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993), and *Panduit Corp.*, 810 F.2d at 1093-94).

The parties agree that the person of ordinary skill is a Ph.D. chemist. Such a person would have paid particular attention to the chemical compounds used in the claimed regimen, especially those that were not previously disclosed, like 2-pyr EHDP. Indeed, P&G agrees that persons of ordinary skill in the art in the mid-1980s sought "more biologically potent [bis]phosphonate compounds that can be administered at low dosage levels which cause little or no mineralization inhibition, thereby resulting in a wider margin of safety." (P&G Br. at 27.) One of ordinary skill in the art seeking a compound with those properties would certainly look to 2-pyr EHDP because it was effective in inhibiting bone resorption at doses lower than any known bisphosphonate, and did not inhibit mineralization at any tested dosage. (Lenz 89; JTX5, col. 13, ll. 20-39.)

The '406 patent describes Schenk and TPTX assays for testing the efficacy of bisphosphonates. (JTX5 at col. 9-11.) The protocols set out in the '406 patent for those assays are the same as those outlined in the '122 patent. (JTX1 at col. 12-14.) The TPTX and Schenk assays in both patents are performed using continuous dosing, and neither patent discloses an assay modified for intermittent dosing. (JTX1; JTX5.) Therefore, a person of ordinary skill in the art would understand that the assay results for 2-pyr EHDP set forth in Tables I, II, and III of the '406 patent indicate that it could be dosed continuously, because it is highly potent and does not inhibit bone mineralization. (JTX5.)

In *In re Inland Steel Co.*, 265 F.3d 1354, 1360 (Fed. Cir. 2001), the court rejected a similar attempt to isolate portions of a prior art reference, holding that a reference must be viewed as a whole, including the non-preferred embodiments. Accordingly, merely

because intermittent dosing is highlighted in claim 15 of the '406 patent does not mean that all other aspects of the document are irrelevant. Indeed, intermittent dosing is highly relevant to the '122 patent, since nothing in the patent claims precludes it. In fact, the practice of the invention of claim 15 of the '406 patent would literally infringe claims of the '122 patent, for example, claims 14 and 21.

4. The '406 Patent Teaches that 2-pyr EHDP Was the Most Potent Bisphosphonate Known

P&G baldly states that the '406 patent does not suggest 2-pyr EHDP over other bisphosphonates described in the same document. P&G ignores what the patent says. Even claim 15 by itself teaches that 2-pyr EHDP is the most promising compound. (McKenna 681-83; Lenz 89.) That claim recommends a dosing strength of "from about 0.00025 mg P/kg to about 0.01 mg P/kg," which is one-tenth the dose recited in the claim for alendronate. (JTX1, claim 15.) The lower end of the range is 1,000 times lower than the corresponding dose for etidronate, 500 times lower than that for clodronate, and 100 times lower than that for pamidronate. That is, claim 15 discloses that for the same use – treatment of osteoporosis – 2-pyr EHDP is ten times more potent than any other known compound (McKenna 683), and hundreds of times more potent than the then-commercially available standard, etidronate.

P&G concedes that the specification of the '406 patent includes 2-pyr EHDP among only eight "preferred" compounds, but argues that it makes no distinction among the compounds in that group. (P&G Br. at 24-25.) P&G is wrong, and not even its witnesses supported that argument. The specification affirms in detail what claim 15 states. It provides exemplary dosing strengths that show that 2-pyr EHDP is the most potent of all the compounds, again by at least a factor of ten. (JTX5, col. 7, ll. 38-68.) It

also includes Schenk and TPTX data which show the order of magnitude difference in activity between 2-pyr EHDP and any other tested compound. (JTX5, Tables I, II and III; Lenz 285-86; McKenna 935-36.) Finally, the specification teaches that 2-pyr EHDP did not inhibit mineralization at any dose at which it was tested. (JTX5, Table III.) Based on these data, there can be no question that the '406 patent teaches that 2-pyr EHDP is the most promising compound of all those disclosed in the patent, and in particular those recited in claim 15. (Lenz 88-90, 96; McKenna 682-84.)

5. The '406 Patent Does Not Disclose Any Toxic Effects That Would Have Deterred a Person of Ordinary Skill in the Art From Selecting 2-pyr EHDP as a Lead Compound

P&G's assertion that the '406 patent teaches that 2-pyr EHDP is lethally toxic is specious. P&G bases its assertion on a parenthetical notation in a footnote to Table III of the '406 patent. (P&G Br. at 25.) That footnote states "compound lethally toxic at 1 mg P/kg/day." (JTX5, col.13:20-38.) As the '406 patent and the evidence presented at trial make clear, the goal in seeking new compounds was to increase a therapeutic window defined as a ratio of a compound's toxic dose to its effective dose. (JTX1, P&G Br at 28.) Since the value is a ratio, a person of ordinary skill in the art would know that the toxic dose means little by itself, and must be viewed together with the effective dose. (Lenz 127-29; Miller 905-06; Eastman 793.) Such a person would recognize that the toxic dose for 2-pyr EHDP was vastly greater than the effective dose, and that the compound's toxicity would be utterly inconsequential. (Lenz 127-29.) Indeed, as Dr. Lenz explained, the toxic dose of Table III is an intravenous dose, while the therapeutic dose is oral. (Lenz 128-29.) Considering the oral bioavailability of bisphosphonates as a class, the therapeutic ratio is 13,000 to one. (*Id.*) Finally, the Schenk data show that the

therapeutic ratio of 2-pyr EHDP is ten times better than that of alendronate, a drug that outsells risedronate by two-to-one. Thus, as described in the '406 patent, 2-pyr EHDP is an incredibly safe drug. (Lenz 129.) Neither of P&G's experts disagreed with Dr. Lenz's assessment.

Proof that a person of ordinary skill in the art would not be deterred by the "lethally toxic" note is found in the specifications and claims of P&G's own patents. Both the '406 and '122 patents claim 2-pyr EHDP as a treatment for bone disease, and give examples of safe and effective doses of that compound for use in human patients.[3] (JTX1; JTX5; Teva USA PFF ¶58.) Neither patent elaborates on the alleged lethal toxicity of 2-pyr EHDP, or gives any indication that it is unsafe. In fact, each patent discloses "safe and effective" amounts for human dosing. (JTX1, col. 12, ll. 1-15, 21-22; JTX5, col. 13, ll. 67 – col. 14, ll. 25.)

Finally, aside from being at odds with the language in its own patents, P&G's argument fails to assess this lethal toxicity issue from the viewpoint of a person of ordinary skill in the art. The only P&G expert witness who testified about the toxicity data in the '406 patent was Dr. Miller, who admittedly did not fit either party's definition of a person of ordinary skill. (Miller 929-30.) The only expert witness from either side who discussed the issue from the viewpoint of a person of ordinary skill in the art was Dr. Lenz, who testified that lethal toxicity of 1 mg P/kg/day in a Schenk test would not prevent 2-pyr EHDP from being an effective pharmaceutical product, and would not have deterred a person of ordinary skill from pursuing it and its variants. (Lenz 285-87.) Dr.

[3] Both alendronate and 2-pyr EDP (a compound that P&G found promising enough to select for development as a drug) are also described as "lethally toxic" in the footnotes to Table III.

Lenz was not alone in his interpretation of the "lethally toxic" language. Dr. Benedict also agreed that that "lethal toxicity" at 1 mg P/kg/day in a Schenk test would not prevent 2-pyr EHDP from being an effective pharmaceutical product. (Benedict 500-03.) Dr. Benedict kept 2-pyr EHDP on his list of preferred compounds after viewing both the Schenk data and the two-day I.V. toxicity screen data. (Benedict 503.) All the evidence indicates that a person of ordinary skill in the art would not be deterred by the parenthetical within a footnote to a table in the '406 patent describing 2-pyr EHDP as "lethally toxic" at 1mg P/kg/day in a Schenk assay; none of the evidence supports P&G's argument.

6. A Person of Ordinary Skill in the Art in the Mid-1980s Would Reasonably Have Expected Risedronate to be Successful in Inhibiting Bone Resorption

Recognizing the similarity between the two compounds, and the clear motivation to modify 2-pyr EHDP to arrive at risedronate, P&G focuses on whether a person of ordinary skill in the art would have had a reasonable expectation of success. P&G argues that a person of ordinary skill in the art could have no expectation whatsoever because the art was highly unpredictable. In view of that unpredictability, P&G asserts, any advance in the field was by hopeless trial and error, such that any bisphosphonate molecule that a skilled artisan conceived of could only ever be "obvious to try." According to P&G's logic, the only motivation that a person skilled in the art would have is to make compounds completely at random, with no rhyme or reason. The corollary of P&G's argument is that not only was risedronate not obvious, but that no bisphosphonate compound or compounds could ever be obvious in view of another.

(a) The Activity of Bisphosphonates Was Not Utterly Unpredictable in the Mid-1980s

As part of its "unpredictability" argument, P&G argues that the mechanism of action of bisphosphonates was not known in the mid-1980s. First, the mechanism of action was not the complete mystery that P&G claims. Dr. Lenz and Dr. McKenna agreed that persons skilled in the art in the 1980s knew that bisphosphonates worked by causing apoptosis (death) of the osteoclast (bone-resorbing) cells. (Lenz 85-86; McKenna 657.) In any event, as Dr. Lenz pointed out, persons skilled in drug discovery generally do not need to know the exact mechanism of a drug's effects, as long as they have ways of testing those effects. (Lenz 86-87.) Here, biological assays were available to measure the activity of bisphosphonates. (Lenz 87, 131.) Persons skilled in the art had available several tests for activity, including the standard Schenk and TPTX tests, as well as screening methods for measuring toxicity. (Lenz 131.)

P&G also asserts, based on out-of-context snippets from the writings of Dr. Fleisch, that no structure-activity relationships existed for bisphosphonates. Dr. McKenna attempted to put bisphosphonates out of the reach of ordinary skill by defining structure-activity relationship as requiring a high degree of knowledge and sophistication. On direct examination, he stated:

> I think that this term is used in different senses in the field. Rigorously a structure activity relationship is a formal study of a fairly significant body of compounds which are varied with respect to some activity, typically a biological activity, which one could correlate in such a way that the activity can be explained by the structure in every case.

(McKenna 564-65.) On cross-examination, however, after agreeing that in fact Dr. Fleisch had related a variety of bisphosphonate structural features to activity, Dr. McKenna conceded:

> Although you might recall at the start of my testimony I mentioned that there is, if you will, a rigorous idea of structural activity relationship and then there is a looser sense which properly is called a structure activity observation.
>
> In other words, obviously if I take six compounds, they will have the same or different activities and now I have a map between these activities and these compounds.

(McKenna 669-670.) Thus, despite his semantic quibble about the difference between "observation" and "relationship," he conceded that persons skilled in the art actually had substantial knowledge of how the bisphosphonate structures contributed to activity. (McKenna 667-72.) Specifically, despite P&G's quotations from Dr. Fleisch, Dr. McKenna conceded that Dr. Fleisch disclosed and others were aware of structure-activity relationships among bisphosphonates. (*Id.*) Such relationships included the fundamental teaching that bisphosphonates as a class inhibit bone resorption. *See* PTX355 at PG191420 ("Indeed, bisphosphonates are extremely effective inhibitors of bone resorption, both in culture and in vivo."). In fact, Dr. Fleisch taught that virtually *all* bisphosphonates were active in inhibiting bone resorption to some degree. *See* PTX356 at PG191254-55 (12 out of 14 compounds tested show activity). He also disclosed that hydroxybisphosphonates are likely to have high activity, and that activity was enhanced by the inclusion of a nitrogen atom in the "tail" of the bisphosphonate molecule. (McKenna 647-48, 670.) Thus, a person skilled in the art, knowing the activity of 2-pyr EHDP, would have known to maintain the integrity of the hydroxybisphosphonate head and to keep the nitrogen atom. (Lenz 106-07.) With those constraints in mind, the simplest modification is the difference between 2-pyr EHDP and risedronate: the point of attachment of the pyridine ring, which is a modification that conserves the basic

molecular structure, the activity-generating portions of the molecule, the molecular weight, the atomic makeup, and the physical state. (Lenz 105-07.)

In the end, P&G's discussion of unpredictability of bisphosphonates misses the point, because it is directed at the predictability of a particular *level* of activity, or a particular precisely defined set of properties. That is not what the law requires. A compound is prima facie obvious if the reasonable expectation is that it will exhibit the same type of activity as the prior art compound at some level, such that the person of ordinary skill would be motivated to make it. No authorities require that the prior art provide the kind of absolute predictability of levels of activities and balance of properties that P&G suggests. *See In re Wood*, 582 F.2d 638, 641 (C.C.P.A. 1978):

> In view of the close structural similarity between the claimed compounds and [the prior art compound]. . . and the fact that the latter is disclosed as possessing antimicrobial activity, we believe that one skilled in the art would have been, prima facie, motivated to make the claimed compounds in the expectation that they, too, would possess antimicrobial activity.

The evidence is clear that virtually all bisphosphonates are active at inhibiting bone resorption to one degree or another. That a compound like 2-pyr EHDP shows markedly superior activity in that regard over all previously known compounds would have provided the motivation to make the small change to create the positional isomer, risedronate. Based on everything the skilled person would know – that the change was small, that most bisphosphonates are active, that the new compound would retain the features (hydroxybisphosphonate head, nitrogen-containing tail) that Dr. Fleisch and others had identified as enhancing activity – that person would have been motivated to make the modification because he or she would have had a reasonable expectation, indeed, a virtual certainty, that the new compound would exhibit bone resorption

inhibition activity. That expectation of activity at some reasonable level made risedronate prima facie obvious.

P&G's "small changes can make big differences" argument (P&G Br. at 28) does not contradict the obviousness of the modification to 2-pyr EHDP. First, equating the difference between water and hydrogen sulfide (one of P&G's prime examples of a "small change") to the difference between 2-pyr EHDP and risedronate is silly. Hydrogen sulfide has approximately twice the molecular weight of water; it has different elements, it exists in a different physical state, and is not an isomer of water. (McKenna 658-59.) Even P&G's bisphosphonate examples for allegedly small changes are not analogous. Unlike 2-pyr EHDP and risedronate, in none of P&G's examples to the compared compounds have the same number of atoms of each element; in none do they have the same molecular weight; and in none are they isomers of each other. (McKenna 657-65.)

Finally, P&G's example of pamidronate and alendronate (P&G Br. at 34) proves Teva USA's argument, not that of P&G. Pamidronate is active in inhibiting bone resorption. (Benedict 432; Lenz 107.) As its close structural similarity to pamidronate would suggest, alendronate is likewise active for the same purpose. (Lenz 107.) P&G points out that alendronate exceeded the expectation that pamidronate promised, and proved to be 100 times more active than pamidronate without exhibiting inhibition of mineralization. (DTX42, col. 13, ll. 35-col. 14, ll. 13.) This vast increase over expectations entitled its developer to a patent. *See Merck*, 228 F. Supp. 2d at 503. As the evidence here makes clear, however, risedronate exhibits no significant advantage over 2-

pyr EHDP. (Lenz 120, 136-37, 145, 148; McOsker 757-58; Miller 882-83, 909-11.) Its patentability cannot rest on the factors cited for alendronate.

(b) Making Different Pyridyl Positional Isomers Was a Standard Technique in Medicinal Chemistry

Not only does going from the 2-pyridyl isomer to the 3-pyridyl isomer represent the smallest and simplest incremental change to the 2-pyr EHDP molecule that preserves the features known to promote activity, it was a modification typically carried out by those of ordinary skill in the art applying medicinal chemistry knowledge and techniques in the 1980s. (Lenz 108.) As Dr. Lenz explained, by the 1980s many successful medicinal chemistry optimizations involved all three pyridyl positional isomers of therapeutic compounds. (Lenz 98-105.) The medicinal chemist's approach in the 1980s involved selecting lead compounds and making changes to them based on established methods. (Lenz 96-97.)

Dr. Lenz showed that the lead compound in the search for an efficacious and safe bisphosphonate would have been 2-pyr EHDP, the most potent compound of claim 15 of the '406 patent. (Lenz 88-90, 285-87.) Since the tail group was known to affect biological activity, the obvious step was to modify it rather than the organophosphorus head portion, which was already optimized. (Lenz 71-72, 106-07.) The tail group on 2-pyr EHDP contains a pyridyl substituent, and Dr. Lenz pointed out, by eight examples of pyridyl positional isomers that were successful enough to be the subject of patents and journal articles, and in many cases brought to market, that this technique was commonplace. (Lenz 98-105.) These prior art examples were not merely ideas of what to "try" but are examples of modifications from which those skilled in the art succeeded. The multiplicity of such successes contributes to the reasonable expectation.

Absolute predictability is not a prerequisite for obviousness. The key is expectation, not certainty. *In re Merck*, 800 F.2d at 1097 ("Obviousness does not require absolute predictability....Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness."); *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 694 F. Supp. 1, 29 (D. Del. 1988) ("the standard does not require 'absolute predictability.'"), *aff'd*, 873 F.2d 1418 (Fed. Cir. 1989). The person of ordinary skill would have expected that risedronate would be active. The high degree of activity of 2-pyr EHDP would have motivated that person to make the simple change to risedronate, with the expectation that the same kind of activity would be preserved. Risedronate was therefore prima facie obvious, and P&G bore the burden of showing that it possessed unexpected significantly advantageous properties compared to 2-pyr EHDP.

7. P&G Failed to Demonstrate "Unexpected Results"

P&G rests its patentability argument primarily on the claim that risedronate shows unexpected results. First, P&G concedes that unexpected results are "secondary considerations." (P&G Br. at 40.) The law is clear that secondary considerations have no place in the obviousness-type double patenting analysis. *Geneva Pharmaceuticals,* 349 F.3d at 1378 n.1. Thus, for Teva USA's double patenting defense, whether risedronate provides unexpected benefits is irrelevant.

P&G then argues that because the art was unpredictable, *any* result would be unexpected, even if not a better one. (P&G Br. at 40.) Even if relevant, however, "unexpected results" for patentability purposes requires that the invention provide an unexpected difference in kind compared to the closest prior art. *In re Merck*, 800 F.2d at 1099; *Monsanto Co. v. Rohm & Hass Co.*, 312 F. Supp. 778, 790 (E.D. Pa. 1970). Thus,

a showing of equivalence to the prior art is not sufficient, nor is a difference along a continuum. Although P&G states that risedronate had "substantially superior testing results" compared to "hundreds of other[] bisphosphonates tested," that information is irrelevant because 2-pyr EHDP is the closest prior art compound. With respect to 2-pyr EHDP, the best P&G showed was rough equivalence. (DTX144 at PG67112; Lenz 120-21, 145, 148; McOsker 757-58.)

To show "unexpected results" P&G relies primarily on its own contemporaneous determination of the lowest effective dose ("LED"). The flaw in this determination, however, is that P&G never tested 2-pyr EHDP at the lowest dose at which risedronate was active. (McOsker 757-58; Lenz 136-37, 145.) In the TPTX test, P&G found that risedronate showed activity at 0.0003 mg P/kg, but P&G never tested 2-pyr EHDP at that low level. (*Id.*; PTX516.) At the next higher level, 0.001 mg P/kg, both compounds showed activity. (PTX514; PTX22; PTX516.) Thus, at the lowest level at which both 2-pyr EHDP and risedronate were tested, both compounds were active, and P&G's TPTX results cannot distinguish between them. (McOsker 757-58; Lenz 135-37, 145.)

With respect to the Schenk test, the results depended on the analytical method used, because the "SPA" method was more sensitive than the "histological" method. (PTX22 at PG23097-98; Lenz 134.) Using the former method, both compounds showed activity at all levels at which both compounds were tested. (PTX518; PTX22.) Again, the data cannot distinguish one from another in terms of lowest effective dose. (Lenz 136-38, 145.) For the SPA analysis, since P&G never evaluated 2-pyr EHDP using that test, no conclusions can be drawn as to which has the lowest effective dose when evaluated using that method. (McOsker 754, 756-58.)

Finally, P&G's experts have no answer for the fact that in P&G's later evaluation, by a third test, 2-pyr EHDP showed three times the activity of risedronate. (DTX36 at 440.) This test and the results from it are described in a paper written by P&G's internal expert, Dr. Ebetino, published in a journal edited by P&G's expert Dr. Miller. Notwithstanding that Teva USA relied on this result, none of P&G's experts or fact witnesses made any attempt to refute it or to explain it away.

That P&G generated this more recent information demonstrating that 2-pyr EHDP is at least as potent as risedronate at a later date not contemporaneous with the making of risedronate is not relevant. The issue is what the fact is: is risedronate unexpectedly more active than 2-pyr EHDP or is it not? All evidence bearing on that issue is relevant regardless of when it was generated. *See Knoll Pharm. Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (data acquired long after patent issued relevant to existence of unexpected properties).

P&G also relies on a presentation of P&G's data that contradicts P&G's own interpretation of the same data that P&G scientists created before litigation provided the motive to spin the numbers to support a legal theory. First, when P&G calculated the histological Schenk data for the purpose of its own internal use and for presentation to the FDA, it concluded by statistical methods that at 0.0003 mg P/kg risedronate had no effect. (DTX144 at PG67112; Miller 945; Lenz 139-45.) For purposes of this case, however, P&G's expert recalculated the numbers by two less rigorous methods, variants of the "Student's" test, and finally found an effect at that low dose. (Miller 862.) Of course, the only thing that this manipulation of the data proves is P&G's willingness to sacrifice accuracy for litigation advantage. In any event, the manipulation is irrelevant,

since P&G never tested 2-pyr EHDP at that level. (Lenz 137.) It is possible that had it done so, it would have found that 2-pyr EHDP was equally active as risedronate or even more so. (Lenz 137-39.)

P&G's second recalculation of the Schenk histological data involves a different way of accounting for the control. Again, when P&G did not see litigation on the horizon, it presented the numbers one way; for trial of this case, it presented them in another manner altogether, so that the minor differences it found the first time are magnified. The plot of data that P&G's authors originally submitted for publication (DTX144 at PG67112) shows that at therapeutically relevant doses the curves for 2-pyr EHDP and risedronate converge, and that even at the highest dose at which both were tested (0.01 mg P/kg), the difference is very small.[4] Although P&G lamely asserted that the original chart was removed before publication, Dr. Miller conceded that the data it plotted were included in the publication's Table VI (DTX74), calculated exactly as shown on the original plot. (Miller 945.) Thus, P&G's comparative presentation shows (1) no comparison at therapeutically relevant doses, (2) no data for 2-pyr EHDP at the lowest dose employed for risedronate, (3) a recalculation designed to favor P&G's litigation hypothesis, and (4) a bias in the data at one dose in favor of P&G's hypothesis.

Nor do the toxicity data show an unexpected benefit. All available data for 2-pyr EHDP show that it was a "very, very safe" drug (Lenz 125, 129), an assessment with which P&G's experts did not disagree. P&G's single two-day screening test, which its own scientist said was not reliable for ranking compounds according to toxicity (DTX114

[4] The result for risedronate at 0.01 mg P/kg was biased upward because of an accidental 100-fold overdose administered to the test animals. (PTX519 at PG191472; Miller 896.) Accordingly, the actual difference is even smaller than shown on the chart.

at PG76987; Benedict 524-25), does not establish an unexpected advantage of risedronate over 2-pyr EHDP. Indeed, P&G's argument conveniently overlooks that in another toxicity screen, 2-pyr EHDP actually showed up better than risedronate. (DTX94 at PG10755-56; Miller 925-26.) At best, the data show that the compounds are both safe at all possibly relevant doses, and that neither compound is better than the other.

P&G bore the burden of establishing an unexpected result. The evidence showed no demonstrable advantage of risedronate over 2-pyr EHDP. At best, the two compounds are equivalent. P&G therefore cannot rely on unexpected results to support the patentability of risedronate.

8. Objective Indicia Do Not Support the Validity of the '122 Patent

(a) Commercial Success Is Irrelevant in This Case

P&G quotes *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988), for the proposition that commercial success should be given its "fair weight." (P&G Br. at 42.) "Fair weight" does not mean great weight, and in some cases can mean virtually no weight. *Merck & Co v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (commercial success "not significantly probative" of obviousness). As in *Merck*, the fair weight that commercial success is entitled to in this case is minimal because it is not significantly probative of obviousness.

P&G discusses at length the evidence which it claims demonstrates the commercial success of Actonel. P&G, however, provides no explanation of how this evidence supports a finding the asserted claims of the '122 patent are valid despite the disclosures of the '406 patent. In fact, P&G attempts to sidestep this critical issue by arguing that the '406 patent is irrelevant, based on its argument that it is not prior art.

(P&G Br. at 45.) Plainly, if P&G is correct, then the statutory obviousness issue is out of the case. If that is true, however, then commercial success is also out of the case because it is a secondary consideration which is irrelevant to Teva USA's other defense, non-statutory or obviousness-type double patenting.

Accordingly, the Court need only address commercial success in the event that the '406 patent is prior art. In addressing the question, however, it is not sufficient merely to look at sales. Commercial success is supposed to be a real-world indicium of whether an invention would have been obvious to persons who were aware of the prior art. *Merck*, 395 F.3d at 1376-77. The economic theory is that if an invention was obvious, the relevant public with knowledge of the prior art and aware of a potential financial benefit by doing the obvious, would in fact have done it. *Id.* That only one party went down a particular path can lead to an inference that the path was not obvious. *Id.* However, if no one else had knowledge of the prior art, it can hardly be surprising that no one else took the action and practiced the claimed subject matter earlier. The inference is inappropriate in this situation. In this case, *only* P&G had knowledge of the '406 patent at the relevant time. Therefore, it is not surprising that only P&G took the obvious step of making risedronate based on its insider's knowledge of 2-pyr EHDP. Thus, the inference that forms the basis for considering commercial success cannot be drawn.

Teva USA's expert economist, Dr. David, is the only economist who reviewed the factual situation in this case. Dr. David's analysis revealed that in this case, in view of the fact that the prior art (the '406 patent) was unknown to the public, the commercial success of Actonel® has no relevance to whether the claimed invention would have been

obvious. (David 297-98.) P&G attempts to dismiss Dr. David's testimony as merely a legal conclusion. Commercial success, however, is an economic issue, and Dr. David's testimony relates to the underlying economic facts that the Court should consider, because only by understanding the underlying economic realities will the Court be able to assign to commercial success its "fair weight." (David 294-99.)

As the Federal Circuit explained in *Merck*, the relevance of commercial success in an obviousness determination depends upon a "chain of inferences"; only where that chain of inferences is complete should commercial success be considered as probative on the issue of obviousness. *Merck*, 395 F.3d at 1377. In this case, the chain of inferences is broken because the relevant public did not have knowledge of the primary prior art reference, and therefore the relevant publics action, or inaction, cannot be tied to what the prior art does or does not teach. (David 297-99.) Where, as here, the primary prior art was unknown, commercial success should be afforded minimal, if any, weight.

(b) Risedronate Did Not Meet Any Long-Felt Needs Where Others Had Failed

P&G asserts that risedronate met a long-felt need for a treatment of osteoporosis, where others failed. P&G claims that such a need existed, that others had tried to solve it, and that risedronate met that need. However, P&G does not address the availability of the primary prior art in evaluating the unmet needs, or the success of others prior to the filing date of the '122 patent. Moreover, P&G fails to present a nexus between the asserted claims of the '122 patent and a solution to the problem of treating osteoporosis.

(i) Long-Felt Need Does Not Apply Because the Prior Art Was Unknown to Others

Since 2-pyr EHDP was not available to those outside of P&G, the long-felt need secondary consideration should carry no weight. The Supreme Court's discussion of secondary considerations in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), relied on a law review article. With respect to long-felt need, that article states:

> The driving force behind innovation is the need for the improvement of existing technology. A defect in a product or process spurs the businessman to deploy resources for discovering a solution. . . . Existence of the defect creates a demand for its correction, and it is reasonable to infer that the defect would not persist were the solution "obvious."

Note, *Subtests of "Nonobviousness": A Nontechnical approach to Patent Validity*, 11 U. PA. L. REV. 1169, 1172 (1964). The underlying assumption includes the availability or accessibility of the prior art and any of its supposed "defects." When the primary prior art reference is not available, the long-felt need consideration should be given less weight. "[E]vidence of actual failures by persons in the art to solve a problem diminishes if those persons could not or did not consider all of the prior art that as a matter of law must be considered in determining obviousness." 3A Donald S. Chisum, Chisum on Patents § 5.05[1][b] n.24 (2006). Here, P&G employees were the only persons skilled in the art who were aware of the closest prior art; others knew nothing of it. As the court stated in *Tennant Co. v. Hako Minuteman, Inc.*, 22 U.S.P.Q.2d 1161, 1180 (N.D. Ill. 1991):

> in the exceptional case where a relevant prior art reference is obscure and not readily accessible, the court should consider the possibility that those who failed to solve the problem were ignorant of the reference. To reason that the failure of others is due to the nonbviousness of the solution regardless of the ignorance of prior art ultimately undermines the validity of the test.

Additionally, since the '406 patent was filed only six months before the '122 patent, P&G's evidence and arguments on this issue all predate the '406 patent filing. Such evidence proves nothing about long-felt need. In *Calmar, Inc. v. Cook Chemical Co.*, the Supreme Court stated: "unsuccessful attempts to reach a solution to the problems confronting [the patentee] made before the appearance of [the primary prior art reference] become wholly irrelevant." 383 U.S. at 36 (*Calmar* is a companion case to *Graham*). In view of the unavailability of the '406 patent, the failure of others to meet the long-felt need does not bear on the obviousness of risedronate.

(ii) P&G Failed to Show an Unsolved Need

P&G's detailed discussion of the state of osteoporosis treatment in the mid-1980s omits that alendronate had been discovered years before the '122 patent filing date. The existence of a long-felt need carries little weight unless that need is unmet. *See Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1988) ("The relevant secondary consideration is 'long-felt *but unsolved need*,' not long-felt need in isolation.") (emphasis added). In situations involving contemporaneous development, courts ask "whether this evidence of contemporaneous development solved the need." *Id.* Although alendronate was not marketed until 1995, it was invented years prior to the '122 patent filing date, making it prior to risedronate and contemporaneous at best. To the extent that the subject matter of asserted claims 4, 16, and 23 of the '122 patent solved the long-felt need for a treatment for osteoporosis, alendronate solved that same exact need, years earlier.

By the time Actonel® became available, alendronate had been on the market for years. Alendronate shares all of the characteristics that P&G asserts made risedronate a

solution to the long-felt need. (*See* P&G Br. at 38-39.) Alendronate has a large therapeutic window, and is much more potent than other prior art compounds in inhibiting bone resorption. It does not inhibit bone mineralization, and has a favorable toxicity profile. (DTX 42 col.13, l.39 – col.14, l.6.) Alendronate continues to be the best-selling bisphosphonate for osteoporosis in the U.S. and in the world, despite risedronate's being on the market for nearly seven years, supported by more than $1 billion in marketing efforts. P&G's own expert, Dr. Bilezikian, stated that alendronate is an outstanding drug that he continues to prescribe to his own patients. (Bilezikian 406.) Therefore, alendronate fulfilled any alleged unmet need prior to risedronate. *See Alza Corp. v. Mylan Pharms., Inc.*, 388 F. Supp. 2d 717, 741 (N.D. W. Va. 2005) (determining that the alleged need the asserted patent met was solved by the prior art).

IV. THE '406 PATENT IS PRIOR ART TO THE '122 PATENT

A. Unwitnessed Notebooks of an Inventor Are Insufficient to Establish Conception

In its brief, P&G asserts that the '406 patent is not prior art to the '122 patent. The '406 patent is based on an application filed on June 6, 1985. Accordingly, it is prior art to the '122 patent under 35 U.S.C. § 102(e) unless P&G can prove that the inventors (Drs. Benedict and Perkins) conceived of the subject matter of claims 4, 16, and 23 in their entirety prior to June 6, 1985.[5]

To prove conception, P&G must show that Drs. Benedict and Perkins possessed in their mind the definite and permanent idea of every limitation of the claimed invention.

[5] P&G fails to address the issue of the availability of the '406 patent under 35 U.S.C. § 102(e), focusing instead solely on section 102(g), which has more stringent requirements.

Kridl v. McCormick, 105 F.3d 1446, 1449 (Fed. Cir. 1997). P&G must make this showing for each asserted claim. P&G has provided no analysis of each claim comparing it to the evidence of record. Instead, P&G merely states that Dr. Benedict had conceived of "risedronate" without any reference to the actual limitations of the claims, and no reference whatsoever to Dr. Perkins.

Proof of conception through the testimony of an inventor requires corroborating evidence that demonstrates that the inventors disclosed to *others* their "complete thought expressed in such clear terms as to enable those skilled in the art" to make the invention. *Id.* at 1449-50. What evidence is required to show corroboration is determined under a rule of reason analysis. *Id.* at 1450. However, this corroboration must include something other than documents created by the inventor, i.e. unwitnessed notebooks of an inventor alone are inadequate to corroborate the inventor's testimony.[6] *See Reese v. Hurst*, 661 F.2d 1222, 1225 (C.C.P.A. 1981) (setting forth the standards for independent corroboration of an inventor's testimony); *see, e.g.*, *Hahn v. Wong*, 892 F.2d 1028, 1032 (Fed. Cir. 1989) ("The inventor, however, must provide independent corroborating evidence in addition to his own statements and documents."); *Chen v. Bouchard*, 347 F.3d 1299, 1311 (Fed. Cir. 2003) (an inventor's notebook was not sufficient corroborating evidence to establish a date of invention).

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[6] P&G asserts that "courts have found that unwitnessed, contemporaneous lab notebooks provide sufficient corroboration" citing to *Medichem S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1169-70 (Fed. Cir. 2006) and *Mahurkar*, 79 F.3d at 1577-78. This is not entirely accurate. In *Medichem* the issue was corroboration of a reduction to practice through an unwitnessed notebook of a *non*-inventor, not corroboration of conception through the unwitnessed notebooks of an inventor. *Medichem*, 437 F.3d at 1172. In *Mahurkar* the court relied upon communications with third parties for corroboration of the inventor's oral testimony, not unwitnessed laboratory notebooks. *Mahurkar*, 79 F.3d at 1578. In neither case did the court rely upon unwitnessed laboratory notebooks of an inventor to corroborate the testimony of an inventor.

In determining conception, the Court should consider all *admissible* evidence, which does not include uncorroborated inventor testimony. While P&G is correct that physical evidence such as unsigned/unwitnessed notebooks do not need to be corroborated, certain minimum levels of proof of conception are still required. For example, unwitnessed laboratory notebooks of an inventor are insufficient, as a matter of law, to establish conception. *Stern v. Trustees of Columbia Univ.*, 434 F.3d 1375, 1378 (Fed. Cir. 2006). In *Stern*, the issue was whether Dr. Stern had conceived of an invention while at Columbia University, and should be granted co-inventor status on a patent that Columbia filed after he left the institution which named another as the sole inventor. *Stern*, 434 F.3d at 1377. The court granted Columbia's motion for summary judgment because the only evidence of Dr. Stern's alleged conception (and therefore his right to co-inventor status) was his uncorroborated oral testimony. Dr. Stern also alleged that his laboratory notebooks, which were not witnessed, would have proved his claims of an earlier conception, but that Columbia had destroyed them. *Id.* at 1378. The Federal Circuit held that even if the documents included the information Dr. Stern claimed, unwitnessed laboratory notebooks of an inventor are insufficient to support a claim of co-inventorship/conception. *Id.; see also Medichem,* 437 F.3d at 1170 n. 8 (quoting *Stern* as applying to conception and co-inventorship status). Similarly, in this case, regardless of what Dr. Benedict's notebooks may or may not state, as a matter of law as they are unwitnessed notebooks of an inventor they are insufficient to support P&G's claims for a date of conception before June 6, 1985.

B. Dr. Benedict's Testimony Cannot Be Considered Because It Is Not Corroborated

As a matter of law, an inventor's oral testimony alone cannot prove conception or reduction to practice prior to June 6, 1985. P&G presented no witnesses who testified regarding any activities of Dr. Benedict prior to June 6, 1985 related to the asserted claims in this case. No witness was provided who could testify that Dr. Benedict indeed conceived of risedronate, let alone each and every limitation of claims 4, 16, and 23, prior to June 6, 1985. The only documents that P&G can rely upon were written by Dr. Benedict himself and not witnessed. Corroboration requires something more than documents generated by the inventor. Accordingly, since Dr. Benedict's testimony was never corroborated (and Dr. Perkins did not even appear at trial), his testimony cannot be considered as a matter of law.

C. The Physical Evidence Relied Upon By P&G Cannot as a Matter of Law Establish Conception

P&G does not present sufficient physical evidence to establish any date of conception prior to June 6, 1985. The physical evidence must be sufficient to show that the inventors had possession of the complete invention as claimed. Further, while physical evidence does not require corroboration, as a matter of law an unwitnessed notebook of an inventor alone cannot support a claim of conception. *Stern*, 434 F.3d at 1378. Each of the pieces of physical evidence that P&G presents is insufficient to establish a date of conception (or reduction to practice) prior to June 6, 1985, taken alone or in combination. P&G points to only 2 pieces of physical evidence (two laboratory notebooks, one unsigned, both unwitnessed) and an alleged shipment to the University of Arizona without any evidentiary support.

1. Unwitnessed Laboratory Notebook PTX67 at PG53521-53522 Is Insufficient to Prove Conception

P&G cites to these pages to support the conception of "risedronate" by Dr. Benedict. (P&G Br. at 8.) These pages are not witnessed and only signed by Dr. Benedict, not Dr. Perkins. Accordingly, as a matter of law these pages are insufficient to support a claim of conception or reduction to practice. *Stern*, 434 F.3d at 1378.

2. Unwitnessed and Unsigned Laboratory Notebook PTX70 at PG54042-54043 Is Insufficient to Prove Conception

P&G cites to these pages in an attempt to prove the alleged recrystallization of "risedronate" by Dr. Benedict, and a purity titration of risedronate in May 1985. (P&G Br. at 7.) These pages are not only unwitnessed, but they are not even signed by anyone, including Drs. Benedict or Perkins. Accordingly, as a matter of law these pages are insufficient to support a claim of conception or reduction to practice. *Stern*, 434 F.3d at 1378.

3. Alleged Shipment to the University of Arizona on June 3, 1985 Is Unsubstantiated

P&G in its brief asserts that "the compound was sent for TPTX testing at the University of Arizona on June 3, 1985." (P&G Br. at 8.) The record contains no support for this assertion, and an analysis of both P&G's brief and proposed findings of fact point out none. To support this claim, P&G points to the uncorroborated testimony of Dr. Benedict that after he first allegedly made risedronate it was sent for testing "shortly after." (Benedict 469.) There is no indication of when it was made, clearly not enough to establish whether this in May, June, July, etc. let alone on June 3, 1985. P&G points to no documents or other evidence that indicate that any shipment was made to the University of Arizona on June 3, 1985. The only document that P&G cites is Dr.

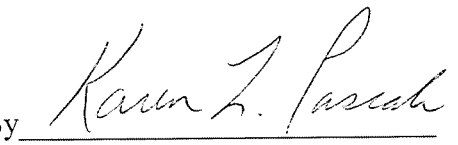
Benedict's notebook, PTX67, at PG53522. Aside from the fact that these pages are not witnessed, they provide no information about the date on which any shipment occurred. As Dr. Benedict testified, the date that this shipment allegedly occurred was not any of the dates listed in the notebook, and nothing else in the notebook indicates when it did occur (if ever). (Benedict 509.) Without *any* evidence of when the alleged shipment occurred, there is no basis for the Court to conclude that it occurred on any date prior to June 6, 1985. Accordingly, this "factual" statement cannot support a finding of conception or reduction to practice prior to June 6, 1985.

CONCLUSION

For the foregoing reasons, and for the reasons set forth in Teva USA's principal brief and proposed findings of fact, the Court should enter judgment that claims 4, 16 and 23 of the '122 patent are invalid.

Respectfully submitted,

YOUNG CONAWAY STARGATT & TAYLOR, LLP

By 

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CERTIFICATE OF SERVICE

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